

The National Birth Defects Prevention Study: An Epidemiological Study of Holoprosencephaly in the U.S.

Sonja A. Rasmussen, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA. Tel: (770) 488-7152, fax: (770) 488-7197, email: skr9@cdc.gov

Birth defects are a leading cause of infant mortality in the United States and contribute significantly to morbidity and long-term disability. The causes of more than 70% of birth defects are unknown, but studies suggest that both genetic and environmental factors are important. Studies of holoprosencephaly have implicated both genetic (e.g., chromosomal and single gene disorders) and environmental (e.g., maternal diabetes) causes. However, problems with previous epidemiologic studies (e.g., small sample size, lack of biological specimens, and lack of consideration of gene-environment interactions) have limited the information known about the etiology of holoprosencephaly.

The goal of the National Birth Defects Prevention Study (NBDPS) is to provide a better understanding of the causes of birth defects. In this ongoing case-control study, case-infants are defined as infants with a major eligible defect (from a list of about 30 eligible birth defects) and are identified from birth defects surveillance systems in eight states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas). Control infants are randomly selected from birth hospital records or birth certificates. Study enrollment began with birth dates or estimated dates of delivery (for pregnancy terminations) of October 1, 1997. Information (including demographics, growth parameters, verbatim diagnoses, diagnostic codes and methods of diagnoses) on case-infants from the eight states is entered into a standardized clinical database, and each case is reviewed by a clinical geneticist. Cases of known etiology (chromosome abnormalities and single-gene conditions) are excluded from the study. Case definition criteria include definitions of defects, diagnostic procedures required for case inclusion, conditions where prenatal diagnosis is acceptable for case eligibility, and specific exclusions. Mothers of case- and control-infants are sent a letter with information about the study and are subsequently contacted via telephone by interviewers to request their participation in the study. After informed consent is obtained, structured telephone interviews lasting approximately 1 hour are conducted in English or Spanish. Interviewers ask about a variety of environmental factors (including infectious, chemical, physical, nutritional, and behavioral factors). Next, a buccal (cheek) cell collection kit is sent to the mother, and specimens on mother, father, and child are requested for use in studies of genetic causes of birth defects. DNA is extracted, and a standardized quality-control protocol is performed on all specimens. The specimens are stored for future use in a centralized facility.

As of February 2002, 10,768 case- and 4,944 control-infants have been identified as eligible for the study. These include 103 case-infants with holoprosencephaly. Of these, mothers of 7,178 cases (including 66 cases of holoprosencephaly) and 3,102 controls have been interviewed. For the more common defects (i.e., orofacial clefts, selected heart defects, and neural tube defects), substantial numbers of cases have already accumulated, and analyses of these data have begun.

The study has several strengths. First, the birth population is large and ethnically and geographically diverse. The case definitions for the birth defects included in the study have been refined to decrease heterogeneity. The interview instrument includes a wide range of potential exposures and confounders. Collection of DNA specimens allows for analysis of genetic factors and gene-environment interactions. The study also has limitations. The study will rely heavily on the ability of mothers to recall exposures, and bias in recall may occur. The amount of DNA collected is small and will limit the number and type of studies possible. We believe this study will provide an invaluable opportunity to study environmental and genetic factors and their potential contribution in the causes of birth defects.

References:

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